

Bandolier to close print editions

Bandolier will cease publishing its monthly print editions after July 2007, making Bandolier 161 the last to appear in print. This was not a decision taken lightly.

One reason was external pressures, particularly several recent hikes in postal charges against a background of never having changed the price from £36 annually. Moreover, many people find it more convenient to download PDF versions from the Internet.

There were internal reasons for making a change, and relieving some of the demands imposed by a monthly printing schedule. Internal changes have combined with different priorities to mark a change in direction.

The Bandolier website will continue, and, we hope, flourish in other ways. Right now Bandolier is looking at how best to continue to re-invent itself electronically after having, to some extent, pioneered universal free access to knowledge.

Looking back, 161 monthly issues of Bandolier will look an awful lot. The initial idea was for three. A huge thank you to faithful readers and correspondents.

On subscriptions

July was chosen as a finish date because that is when most subscriptions (about 70%) are renewed. Bandolier has stopped accepting new subscriptions. For people who renewed in March, we will continue to send Bandolier out to the last issue, but will not cash any payment.

Those with longer subscription periods unfilled are requested to contact the Bandolier subscriptions office (maura.moore@pru.ox.ac.uk) to claim any rebate.

In this issue

H-index.....	p. 1
Epidural and risk: it all depends	p. 2
Value of vision.....	p. 4
Avastin or Lucentis.....	p. 5
Race, anaemia, and mortality.....	p. 6
Activity levels and type-2 diabetes risk.....	p. 7
Persistence with bisphosphonates.....	p. 8

H-INDEX

Bibliometrics is all about methods used to study texts and information. Much of it, though not all, is about citations, especially as it applies to citation analysis, which we use when looking at journal impact factors (Bandolier 118). Some aspects of bibliometrics have become important for pointy-headed academics because they are used to measure academic worth. Getting papers published in high impact factor journals has become more important than the total number of papers published in some schemes of measurement.

There is now a new kid on the block, and pointy-heads need to sit up and take note. It is the H-index (or Hirsch number [1]), which is much more personal, and is based on the number of citations that each from an author's articles receives. The definition is the following:

A scientist has index h if h of his/her N_p papers have at least h citations each, and the other ($N_p - h$) papers have fewer than h citations each.

Put simply, a scientist with an index of X has published X papers with at least X citations each. Someone with an H-index of 20 has 20 papers cited more than 20 times each.

H-index importance

It is quite easy to find citation numbers, either through the Science Citation Index, or, more simply, through Google Scholar. A few papers have astronomical citation numbers (thousands), some have hundreds of citations, more have tens, and most have just a handful. The H-index is a clever way to establish how much *impact* a researcher has had.

What's good

Nobel prizewinners in physics had H-indices of 20-80. In medicine the index tends to be higher, but the highest is reputed to be about 190. An H-index of about 40-50 should get you admitted to the US Academy of Sciences. An index of 20+ is pretty good for most researchers. Of course there are criticisms of any way of measuring worth, but the H-index is easy to calculate and seems to make immediate sense.

Reference:

- 1 JE Hirsch. An index to quantify and individual's scientific research output. Proceedings of the National Academy of Sciences 2005 102: 16569-16572.

EPIDURALS AND RISK: IT ALL DEPENDS

Risk: it all depends, doesn't it? It's one of those irregular verb things, is risk; I am a perfectly safe driver, you are a bit dodgy, he is an accident waiting to happen. But if I drive a modern car with seat belts and airbags, at moderate speed, on quiet roads, during the day, while you drive an old banger on the motorway, and he drives an even worse banger without seatbelts home from the pub when dead drunk, the point is made. It all depends.

When it comes to risks in medical procedures, it all depends, but we don't often have examples of just how much the setting can change the risks. For at least one example we now have an inkling of the effect of setting.

Bandolier 152 discussed the risks following use of an epidural during childbirth. Briefly, there was a risk of deep epidural infection in 1 in 145,000, epidural haematoma in 1 in 170,000, and persistent neurological injury lasting more than one year in 1 in 240,000 women. The rates were abstracted from larger observational studies, and the risk came both from spontaneous occurrence and from the epidural catheter and anything injected through it, but combining all of them the risks were low.

Two further systematic reviews [1,2] have examined similar outcomes in two very different circumstances, postoperatively after cardiovascular surgery, and in chronic pain.

Systematic reviews

The methods of the two new systematic reviews [1,2] were similar to those described for obstetric patients in Bandolier 152. The same outcomes were sought, namely epidural haematoma, infection, and neurological injury in the shorter (less than one year) and longer term. Studies with fewer

than 200 patients were not sought, as they were unlikely to report on rare events, and case reports would be unlikely to have a denominator to calculate rate.

Results

Table 1 reprises the main findings for the four outcomes in all three settings, as well as providing brief information about the patients, duration of epidural catheter use, and number of patients on whom information was available. The "rule of 3" (Bandolier 23) was used to calculate maximum event rates when there were no events; this says that the upper 95% confidence interval that the event will not occur is 1 in the total divided by three (n/3).

Cardiovascular surgery

In 12 studies were 14,105 patients, of whom 5,026 (36%) had vascular surgery, 4,971 (35%) cardiac surgery, and 4,108 (29%) thoracic surgery. There were no cases of epidural haematoma (Table 1), giving maximum (worst case) risks following epidural anaesthesia in cardiac, thoracic, and vascular surgery of 1 in 1,700, 1 in 1,400 and 1 in 1,700 respectively.

In all these surgery types combined the maximum expected rate would be 1 in 4,700. In all these patients combined there were eight cases of transient neurological injury, a rate of 1 in 1,700 (95% confidence interval 1 in 3,300 to 1 in 850). There were no cases of persistent neurological injury (maximum expected rate 1 in 4,700).

Chronic pain

In this chronic pain review epidural catheters had to be in place for seven days or more. Twelve studies provided information on 4,628 patients. There was no information on epidural haematoma or neurological injury.

Table 1: Risks associated with epidural catheter in different circumstances

		Obstetric	Cardiovascular	Chronic pain
Duration of catheter (days)		<2 days often single shot	<2 days anticoagulated	>10 days (average 74)
Number of patients		1,370,000	14,100	4,600
Epidural haematoma	Number of events	6	0	
	Risk	1 in 168,000	1 in 4,700	
Deep infection	Number of events	11		57
	Risk	1 in 145,000		1 in 80
Neurological injury >1 year	Number of events	3	0	
	Risk	1 in 240,000	1 in 4,700	
Neurological injury <1 year	Number of events	254	8	
	Risk	1 in 6,700	1 in 1,700	

Figure 1: Deep infection rates in individual studies of patients with chronic pain

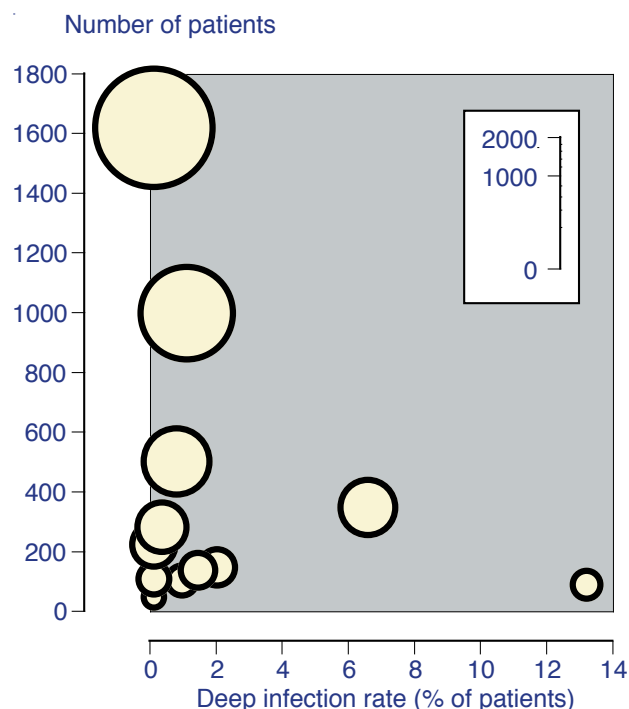
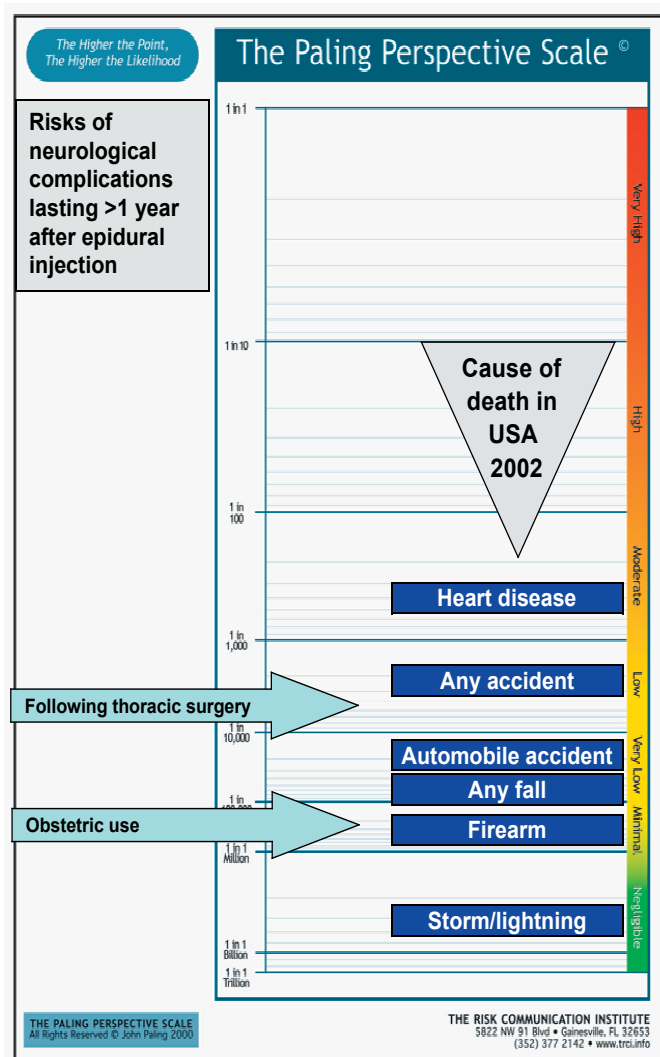


Figure 2: Paling perspective scale showing risk of long term neurological problems with epidural catheter with obstetric use and in thoracic surgery



There were 57 deep infections (1.2%). Ten of the 12 studies had deep infection rates of 2% or less (Figure 1). The incidence of deep infection was 1 per 2391 days of treatment, or 0.4 per 1000 catheter treatment days. In nine studies (1503 patients), predominantly in cancer, and with average catheter duration of 74 days, the deep infection rate was 2.8%. The proportion of patients with infection of any type was higher in cancer patients with longer catheter duration.

Comment

It is obvious that the three situations are not the same. Obstetric epidural use involves young, mainly healthy, women in whom epidural catheters are used mainly for a short period. Cardiovascular patients will tend to be older, and sicker, and while epidural catheters will generally be used only for a few days, anticoagulation will make their use more risky. In chronic pain, very long term use is often in very ill patients.

In these three circumstances our evaluation of the risk understandably differs. The most glaring difference is the amount of information we have, with 100 times more for obstetrics than cardiovascular surgery. This makes any estimate of risk more credible.

Indeed, the number of events was so few for cardiovascular surgery and chronic pain settings that we have to invoke the rule of three to estimate a maximum risk. Some events were just not reported in chronic pain patients, probably because they were not very important in the circumstances.

As best we can judge, the risks themselves differ between circumstances. Figure 2 shows the estimated risk of neurological injury lasting one year or more in obstetrics and cardiovascular surgery using a Paling Perspective Scale. The carry home message, though, is not how good we are at estimating risk, but about how little we seem to know.

References:

- 1 W Ruppen et al. Incidence of epidural haematoma and neurological injury in cardiovascular patients with epidural analgesia/anaesthesia: systematic review and meta-analysis. BMC Anesthesiology 2006 6:10.
- 2 W Ruppen et al. Infection rates associated with epidural indwelling catheters for seven days or longer: systematic review and meta-analysis. BMC Palliative Care 2007 6:3.

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VALUE OF VISION

These days it's all about cost. That's what many people think about modern medicine. Others, and most health economists and purchasers would say, au contraire, it's all about value. The most expensive medicine, they would say, is the one that doesn't work. Yet others, perhaps those giving a tad more deep thought, would point out that no medicine works in every patient, and perhaps if we could discover which patients would benefit from which medicine we might do rather better for all of them.

While the argument rages, or mumbles, on, we are stuck with a definition of good value that works out, for a quality-adjusted year of life (QALY) of about £30,000 or \$50,000 or less. These are not easily calculated, and lead into some very convoluted paths, as the example of age-related macular degeneration (ARMD) demonstrates [1].

Visual value

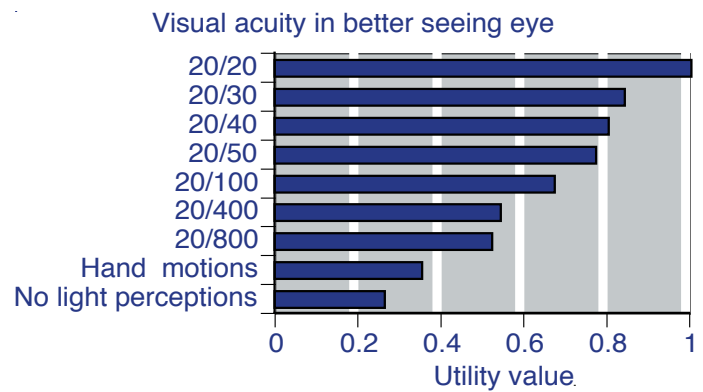
We measure vision most commonly by visual acuity, a quantitative measure of the ability to identify black symbols on a white background at a standardized distance as the size of the symbols changes. Visual acuity is the smallest size that can be reliably identified. The well-known phrase "20-20 vision" refers to the distance in feet that objects separated by an angle of 1 arc minute can be distinguished as separate objects. The metric equivalent is 6-6 vision.

20/20 means one can see small letters, 20/40 moderate letters only but not small ones, while 20/100 means that only the very largest letters can be distinguished at 20 feet, but that someone with normal vision would be able to distinguish these letters at a distance of 100 feet. As the second number increases, then, visual acuity gets worse.

A review [1] brings together some aspects of the way we value vision. For instance, Figure 1 shows the time trade-off utility values for different levels of visual acuity, where a value of 1 is normal health and zero death. Here people are asked how many years of remaining life they would trade for permanent normal health. People with a moderate reduction in acuity to 20/40 say they would be willing to trade four of 20 remaining years of life for a return to normal visual acuity (1.0 minus $\{4/20\}$).

Clearly, impaired vision impacts significantly on health utility, but the degree by which vision is valued is under

Figure 1: Time-trade utility values for different levels of visual acuity



appreciated by the public, clinicians in general, and ophthalmologists in particular (Table 1). Ophthalmologists, for instance, considered that patients would be prepared to lose 2% of available life years to return to 20/20 vision from 20/40, which is what a utility value of 0.98 says in Table 1. By contrast, patients were prepared to lose 17% of their remaining time of life (utility = 0.83).

Comparison with other conditions

Visual acuity of <20/200 in the better eye (severe ARMD) has utility values similar to severe stroke, or advanced prostate cancer with uncontrollable pain. Moderate ARMD (20/50 to 20/100) has similar utility values to moderate stroke or a hip fracture. Mild ARMD has similar utility values to vertebral fractures or symptomatic HIV.

When value gains are compared between some interventions for macular degeneration and interventions for other conditions (Table 2), it is clear that they compare well in terms of quality or length of life.

Comment

This particular paper [1] is not one that Bandolier would normally consider for its pages. It is not a systematic review, and though it does look at quality of evidence, there are some deficiencies in the amount of evidence available. But it does make one think, and for that reason alone is worth a quick read. For those engaged in the difficult decisions around value and cost for different interventions, it is probably worth a more detailed read, especially with some effective but perhaps costly therapies coming our way.

Table 1: Time-trade utility values given by patients and others for different levels of age-related macular degeneration severity

ARMD severity	Utility values			
	Patients with ARMD (n=82)	Community (n=142)	Clinicians (n=62)	Ophthalmologists (n=46)
Mild (20/20 to 20/40)	0.83	0.96	0.93	0.98
Moderate (20/50 to 20/100)	0.68	0.92	0.88	0.89
Severe (20/200 or worse)	0.47	0.86	0.82	0.73
Very severe (<20/800)	0.39	not available	not available	0.67

Table 2: Value gain in quality or length of life for interventions in age-related macular degeneration and other conditions

Intervention	Value gain (%)
Interventions for macular degeneration	
Laser photocoagulation; subfoveal classic	4.4
Laser photocoagulation; extrafoveal classic	8.1
Photodynamic therapy	8.1
Intravitreal pegaptanib	5.9
Intravitreal ranibizumab	>15
Interventions for other conditions	
Bisphosphonates for osteoporosis	1.1
Alpha-blockers for BPH	1 - 2
Statins for hyperlipidaemia	3.9
Beta-blockers for hypertension	6 - 9
PPI for reflux	11

Reference:

- 1 MM Brown et al. Value-based medicine and interventions for macular degeneration. *Current Opinion in Ophthalmology* 2007 18: 194-200.

LUCENTIS VS AVASTIN: NEEDS MUST OR DEVIL DRIVES?

Every so often an issue pops up its head that we are glad not to have to deal with. One such involves a new treatment for age-related macular degeneration.

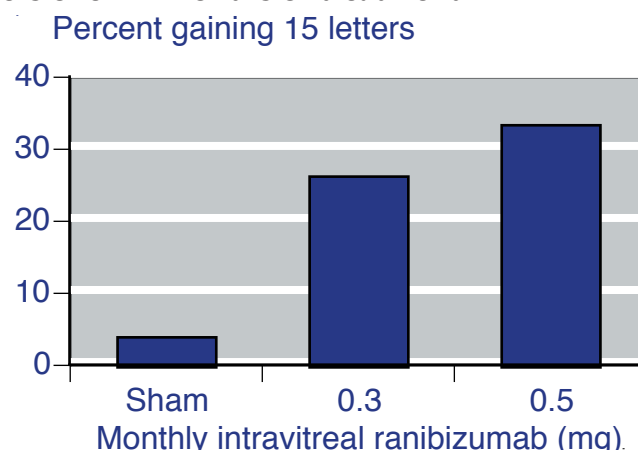
New monoclonal antibodies against vascular endothelial growth factor (VEGF) have been shown to reduce choroidal neovascularisation of ARMD, because VEGF helps promote endothelial cell growth and increases vascular permeability. The antibodies usually have to be given by intravitreal injection, usually at intervals of a month or so. The result is prevention of vision loss and improved mean visual acuity [1].

In a large (716 patients), long (two year), randomised comparison of intravitreal ranibizumab 0.3 mg and 0.5 mg versus sham injections, significantly more patients gained 15 or more letters with ranibizumab (Figure 1). The NNT for a gain of 15 letters over two years was about 3 for 0.5 mg and 4 for 0.3 mg.

The problem

There are two sources of anti-VEGF monoclonal antibodies. One is ranibizumab (Lucentis), which is licensed for intravitreal injection in ARMD. The other is bevacizumab (Avastin), which is licensed for intravenous infusion in metastatic colorectal cancer. Avastin contains anti-VEGF monoclonals at much higher dose than for intravitreal injection, so many

Figure 1: Percent of patients with age-related macular degeneration gaining at least 15 letters over 24 months of treatment



intravitreal doses could be made from a single intravenous dose. In consequence, while ranibizumab (Lucentis) costs \$2,000 per intravitreal injection, bevacizumab (Avastin) costs \$50 for an equivalent dose.

What makes them different, as the manufacturer would tell us, includes the following:

- Avastin contains no preservatives, so there could be problems in keeping it sterile when split into small quantities required for retinal treatment.
- No pre-clinical trial toxicity data exists for use of Avastin in retinal therapy.
- The half-life of Avastin is different from Lucentis, in that it clears from the system 100 times slower. This is important for cancer use, but remaining in the retina for that length of time could be harmful.
- Lucentis binds more strongly to the VEGF protein than Avastin. It is this binding that blocks the protein from developing blood vessel growth into the retina (neovascularization).
- Avastin contains full-length antibodies, which can cause inflammation. The antibody fragments in Lucentis are 1/3 the size of Avastin antibodies, so they are capable of better penetration through the retinal layers.
- Manufacturing standards differ for cancer and ophthalmic drugs. Particulate matter must be very low in drugs used in the eye, and Avastin is not manufactured with that in mind.

It is also the case that there are some small case series, but no randomised trial evidence exists for benefit from bevacizumab (Avastin), nor much at all for harm, especially rare but serious harm.

The costs

These have been modelled in detail [2] to compare the costs and impact of these alternatives. Basically, to hit the NICE threshold of £30,000 per QALY, bevacizumab (Avastin) would have to be half at least as effective as ranibizumab (Lucentis). If the price of ranibizumab (Lucentis) was reduced by 75%, bevacizumab would have to be 5% more effective to achieve this threshold.

Based on about 25,000 new cases of neovascular ARMD a year in the UK, treatment with ranibizumab (Lucentis) would cost £300 million a year. Substituting with bevacizumab (Avastin) would save £292 million.

Comment

Both drugs come from the same company. That company would argue that the price reflects the cost of development and production. The problem for authorities like NICE, which has to make some difficult decisions over this, is that it has in the past argued against off-licence use of drugs. It would be a difficult philosophical position to change.

On the one hand we have reasonably good evidence for effect and safety over a long period, but with a high cost. On the other we have no good evidence of effect or safety, but at low and affordable cost. It makes for a difficult decision. A sensible resolution is required, perhaps a third way?

References:

- 1 PJ Rosenfeld. Ranibizumab for neovascular age-related macular degeneration. *New England Journal of Medicine* 2006 355: 1419-1431.
- 2 J Raftery et al. Ranibizumab (lucentis) versus bevacizumab (avastin): modelling cost effectiveness. *British Journal of Ophthalmology* 2007 DOI 10.1136/bjo.2007.116616

RACE, ANAEMIA, AND MORTALITY

Anaemia and mortality has been looked at before by Bandolier (138, 146). We know that anaemia is more common in older people, and perhaps more in women than men, and there have been indications of some racial differences as well. A new study [1] not only confirms some of the racial differences in anaemia prevalence, but also indicates that the consequences of anaemia may differ according to race.

Study

The study included people aged 70-79 years in Memphis and Philadelphia who were living in the community, could walk a quarter of a mile without difficulty, climb stairs without resting, and were performing basic activities of daily living. Exclusions included use of a walking device, treatments for cancer, or being in a clinical trial. In 2000 baseline haemoglobin values were assessed in 2,601 people, and anaemia assessed using the WHO criteria of <120 g/L for women and <130 g/L for men. Race was self-reported.

Mortality was the primary outcome over the period to August 2005. A secondary outcome was mobility disability.

Results

The population was about 50% women and 40% black, and the mean age was 75 years. Compared with white people, black people had a higher BMI, had better renal function, and were less likely to have cancer, but more likely to have coronary heart disease, diabetes, ulcers, and hypertension.

For women and men, mean haemoglobin concentrations were about 10 g/L lower for blacks than whites. More black people had lower haemoglobin levels than white people (Figures 1 and 2). WHO defined anaemia was found in 21% of black women compared with 7% of white women, and 26% of black and 14% of white men.

Mortality was significantly higher among black women and men than white (Figure 3). Mortality was not affected by the presence of anaemia in black women and men, but

Figure 1: Distribution of haemoglobin concentrations in black and white women

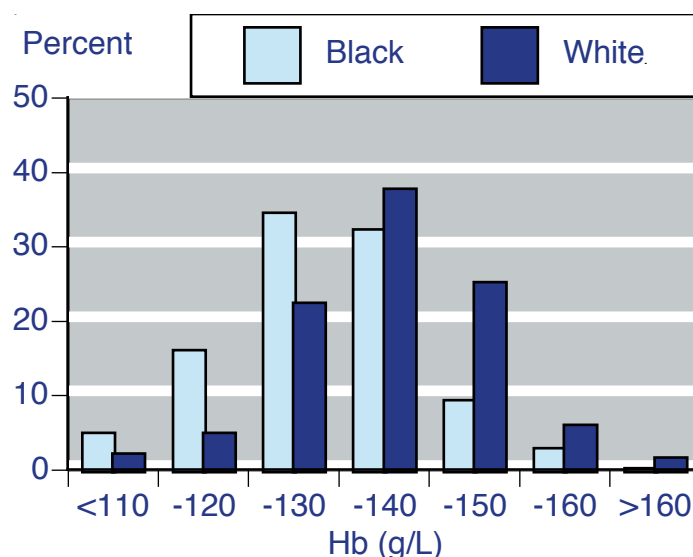


Figure 2: Distribution of haemoglobin concentrations in black and white men

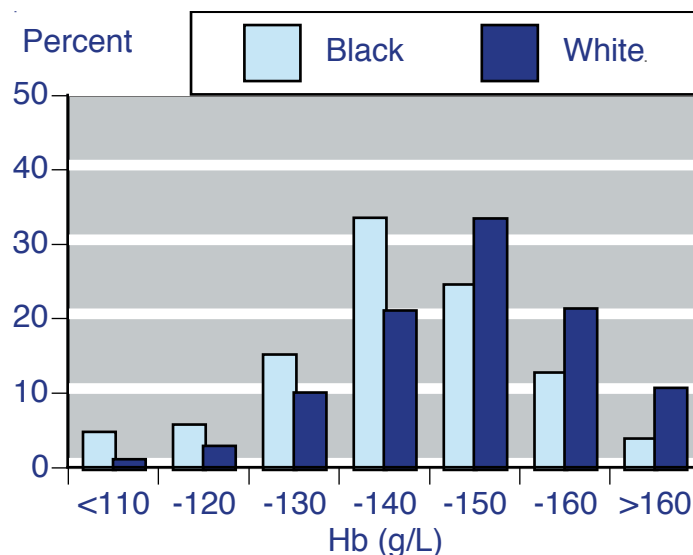
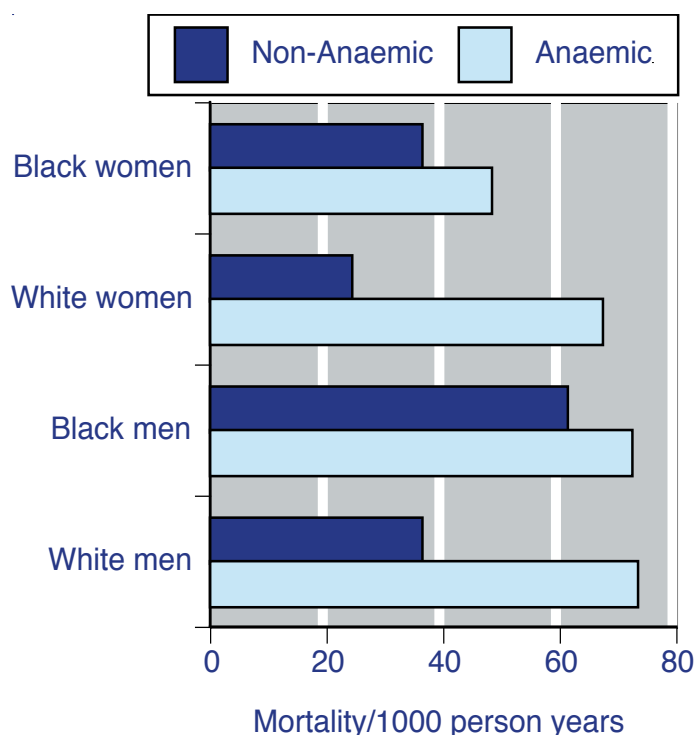


Figure 3: Mortality (per 1,000 patient years) according to anaemia status, sex, and race



was significantly higher in white women and men with WHO-defined anaemia. An eGFR below 60 mL/min/1.73 sq m was associated with higher anaemia mortality in blacks and whites.

Developing mobility disability was also significantly associated with anaemia in white women and men, but not in blacks.

Comment

When considering anaemia in older people, we may need to take more account of race. This study looked only at black and white people, as they defined themselves. There was no category for Asian or other ethnic origins.

For older black people, we may need to revisit the WHO criteria and come up with race-specific criteria. It certainly appears that black men and women function reasonably well at lower levels of haemoglobin and better than their white counterparts.

We also need to be careful about mortality rates. While there is a significantly greater mortality with anaemia, this appears to have more to do with lower rates of death in white women and men who were not anaemic than higher death rates in anaemic black women and men. The difference in mortality being anaemic and non-anaemic seems to be bigger in white women and men than in black women and men.

References:

- 1 KV Patel et al. Racial variations in the relationship of anemia with mortality and mobility disability among older adults. Blood 2007 DOI 10.1182/blood-2006-10-055384

MODERATE ACTIVITY REDUCES DIABETES RISK

Hands up everyone who knows what a MET is? Answer is a Metabolic Equivalent Task, which is the amount of energy expended in performing various activities compared with sitting down doing nothing. It is commonly used in medicine to express metabolic rates measured during a treadmill test. Two definitions of the MET are used, essentially equivalent:

1 MET is equivalent to a metabolic rate consuming 3.5 millilitres of oxygen per kilogram of body weight per minute.

1 MET is equivalent to a metabolic rate consuming 1 kilocalorie per kilogram of body weight per hour.

In more common parlance, a slow walk or promenade is equivalent to about two METs, a brisk walk about four METs, and gym work more like six METs and above. A new systematic review of observational studies links moderate periods of moderate intensity exercise with reduced risk of developing type 2 diabetes in adults [1].

Systematic review

The review sought observational studies up to March 2006 associating moderate exercise with incidence and prevalence of type 2 diabetes. Moderate intensity exercise was that with a MET score of 3-6.

Results

Ten cohorts were found with just over 300,000 persons of both sexes aged mostly between their late-30s to early-60s. Follow up in these studies tended to be long with seven of the studies longer than seven years, and the shortest four years. The mean follow up period, weighted by study numbers, was 8.2 years.

In most of the studies exercise included walking, but cycling and light gardening were also included. The definition of diabetes varied, including glucose tolerance test results, the use of primary care or national registers, and, mostly, by self-report of a diagnosis by a physician, usually validated.

There were 9,400 cases of diabetes, a prevalence of 3.1%. This meant that type 2 diabetes occurred in 0.4% of these older adults every year, a risk of 1 in 263 per year. Compared with sedentary persons, the risk was substantially lower in people who took moderate exercise (by about 30%), whether all activity or only brisk walking was used in the tests of association (Table 1). Because people who take no exercise tend to be fatter, there was adjustment of risk for BMI, and here the reduction of risk was about 17%.

Comment

The amount of exercise examined in this paper was not heroic, amounting to no more than about 2.5 hours of brisk walking every week. The message is that to help avoid developing diabetes, you don't necessarily have to go into

Table 1: Evidence associating physical activity and walking with reduction in risk of developing type-2 diabetes

Observation	Studies	People	Relative risk	Percent risk reduction
Total physical activity				
Development of type 2 diabetes, no BMI adjustment	9	213,314	0.69 (0.58 to 0.83)	31
Development of type 2 diabetes, with BMI adjustment	9	295,231	0.83 (0.76 to 0.90)	17
Walking				
Development of type 2 diabetes, no BMI adjustment	4	152,698	0.70 (0.58 to 0.84)	30
Development of type 2 diabetes, with BMI adjustment	4	234,615	0.83 (0.75 to 0.91)	17

the gym, just walk down there and then walk back again. Given that walking does other good things positively affecting heart, and circulation, and bone, and balance, and weight, this is something of a no-brainer. Diabetes is worth avoiding.

References:

- 1 CY Jeon et al. Physical activity of moderate intensity and risk of type 2 diabetes. *Diabetes Care* 2007 30: 744-752.

PERSISTENCE WITH BISPSPHONATES

Bandolier looks for good information on persistence (compliance, concordance, adherence, whatever) because medicines work better in the patient than in the blister pack. For so many long-term therapies persistence is awful. With bisphosphonates one reason is the boring way bisphosphonates have to be taken; fasting overnight, taken alone, lots of water, no other food or drink and remaining upright for 30 minutes. Lack of motivation in an asymptomatic disease contribute to the "why bother?" factor. A systematic review [1] shows that reducing hassle improves persistence.

Systematic review

The review looked at a single database (1998-2006) for anti-osteoporosis medicines using terms relating to compliance or persistence. Studies had to have one measure of compliance or persistence derived from administrative databases with patient demographic and prescription information.

Compliance (defined as the extent to which a patient acts in accordance with the prescribed interval and dose as well as dosing regimen) was measured as the medication possession ratio (MPR). This is the number of days' supply received over the length of the follow up, and is described as a ratio. Persistence (defined as the accumulation of time from initiation to discontinuation of therapy) was measured as the number of days of possession without a gap in refills, and the percentage of patients.

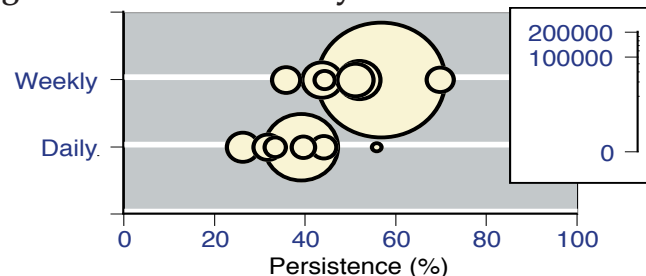
Results

Most of the therapies in the 14 studies obtained were for oral daily or weekly bisphosphonates. Studies had observation periods mainly of one year, with some longer. Results for daily or weekly bisphosphonates are shown in Table 1. All of the compliance and persistence outcomes were better for weekly than daily bisphosphonates. Clearly this was obvious to most prescribers, as the number of persons prescribed weekly bisphosphonates was five times higher than those prescribed them daily.

Table 1: Daily and weekly bisphosphonate

Information/outcome	Daily	Weekly
Number of subjects	41,952	197,536
Medication possession ratio (MPR)	0.54	0.64
Persistence (days)	192	237
Persistence (%)	38	56

Figure 1: Individual study results



While Table 1 shows the average results weighted by number of patients, Figure 1 shows the individual study results for the percentage of patients compliant, which was consistently higher for weekly than daily use.

Comment

Not earth shattering, but solid evidence that making things easier for patients can help. The paper has an interesting discussion about how different methods of measuring persistence and compliance can affect results, all of which is interesting. The simple fact, though, is that weekly bisphosphonates resulted in higher use. It is likely that high compliance and persistence are needed to minimise fracture risk.

Reference:

- 1 JA Cramer et al. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporosis International* 2007 DOI 10.1007/s00198-006-0322-8.